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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/092,849	03/07/2002	David D. Frisbie	CSUA:026--10606.0026.PCUS	9447

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S.A.M.

Office Action Summary	Application No.	Applicant(s)	
	10/092,849	FRISBIE ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-36 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-36 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 3/7/02.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-36 are pending in the present application, and they are examined on the merits herein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davidson et al. (U.S. Patent No. 5,747,072; IDS) in view of Kato et al. (Veterinary Immunology and Immunopathology 56:221-231, 1997; IDS).

The claims are drawn to methods to reduce the effects of joint disease in a mammal, to increase the influx of white blood cells into the joint of the mammal, to

increase the percentage of neutrophils in the joint of a mammal, to decrease the percentage of mononuclear cells in the joint of a mammal, to produce interleukin-1 receptor antagonist protein in vivo, to delay the onset of joint disease in a mammal, said methods comprise the steps: selecting a mammal suspected of having a joint afflicted with a joint disease or a mammal comprising a joint for treatment; and administering one or more viral particles to the joint by arthrocentesis, wherein the viral particles comprise a nucleic acid sequence encoding an equine interleukin-1 receptor antagonist protein.

Davidson et al. teach methods of transferring a gene to a synovial cell by transducing the synovial cell *in vivo*, with a recombinant adenoviral vector as well as methods of treating an inflammatory condition (e.g., osteoarthritis and rheumatoid arthritis) in the joint of a subject comprising administering to the joint a therapeutically effective amount of a recombinant adenoviral vector having an expression control sequence operatively linked to a gene that encodes an anti-inflammatory sequence (see abstract and Summary of the invention). Davidson et al. teach that IL-1β is a protein mediator of inflammation, and therefore IL-1 antagonists are anti-inflammatory agents, and that IL-1 receptor antagonist is a potent anti-inflammatory agent, with human IRAP used in the exemplification (col. 4, lines 8-11; example II). Davidson et al. further teach that the subject includes mammals (e.g., a rabbit) or humans (col. 4, lines 41-42, and example II); and proper dosages may be established using clinical approaches familiar to the medicinal arts and that dosages include about 10^7 to 10^{13} particles of viral vector per ml of carrier (encompassing the recited dosage of 10^9 viral particles), with approximately 10^{10} adenoviral particles suspended in about 1ml of sterile PBS

constitute a therapeutically effective amount (col. 4, lines 56-67). The recombinant adenoviral vector is administered by intra-articular injection (or arthrocentesis) because it provides superior access to the joint by the therapeutic agent (col. 4, lines 47-50).

Davidson et al. do not specifically teach the use of viral particles comprising a nucleic acid sequence encoding an equine interleukin-1 receptor antagonist protein, or a method of treatment wherein the treated mammal is a horse.

However, at the effective filing date of the present application, Kato et al. already cloned and characterized a cDNA encoding for an equine interleukin-1 receptor antagonist protein (eqIRAP) to establish a basis for cytokine therapy of acute and chronic inflammatory diseases in the horse (see abstract). The eqIRAP shares conserved structural similarities with human, murine and rabbit IRAPs and therefore eqIRAP shares the basic biological functions that IRAPs exhibit in the other species. EqIRAP was shown to inhibit the cytostatic or cytotoxic activity of IL-1 on human A375S2 cell line. Kato et al. further teach that equine IRAP cDNA and recombinant protein could be useful not only for investigating equine inflammatory diseases but also for treatment by administering the recombinant IRAP and IRAP gene transfer, particularly because arthritis is a serious problem in racing and riding horses (page 229, third full paragraph).

Accordingly, it would have been obvious for an ordinary skilled artisan at the effective filing date of the present application to modify the methods taught by Davidson et al. by delivering *in vivo* a recombinant adenovirus encoding an equine IRAP into a mammal or a horse for treatment purposes or for investigation of equine inflammatory

diseases in light of the teachings of Kato et al. because equine IRAP shares the basic biological functions as other IRAPs from other species, and that arthritis is a particularly serious problem in racing and riding horses. The modified methods resulting from the combined teachings of Davidson et al. and Kato et al. are indistinguishable from the methods of the presently claimed invention in terms of the method steps and starting materials.

An ordinary skilled artisan would have been motivated to carry out the above modification because IL-1 receptor antagonist (IRAP) is a potent anti-inflammatory agent as taught by Davidson et al., and that equine IRAP shares the basic biological functions as other IRAPs from other species as taught by Kato et al. Additionally, arthritis is a particularly serious problem in racing and riding horses.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Davidson et al. and Kato et al., as well as a high level of skill of an ordinary artisan in the art of intra-articular injection of a recombinant vector comprising a sequence encoding IRAP into a mammal.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glorioso et al. (U.S. Patent No. 6,159,464) in view of Kato et al. (Veterinary Immunology and Immunopathology 56:221-231, 1997; IDS).

Glorioso et al. teach a method for treating a connective tissue disorder by introducing at least one gene encoding a product into at least one target cell of a joint or a mammalian host, including a human or a rabbit (col. 11, lines 55-60, and examples XV-XVII). Glorioso et al. teach that a gene of interest includes an interleukin-1 receptor antagonist gene, fragment or its derivatives as long as its encoded protein, fragment or derivatives can still function in the same manner as the wild type IRAP (col. 13, lines 1-29; col. 14, line 64 continues to line 24 of col. 15). The gene of interest is delivered directly (e.g., intra-articular injection) into a joint of a mammal in the form of various viral vectors such as an adenovirus, a retrovirus, an adeno-associated virus, a herpes virus as well as non-viral vectors (col. 17, lines 44-49; col. 19, lines 51-57). Glorioso et al. also teach that injections of recombinant adenovirus **exceeding** 1 x 10^9 pfu (this represents at least 1 x 10^9 viral particles) proved inflammatory in naive rabbit joints, and exacerbated the pathology in knees with antigen induced arthritis (a.i.a.), greatly increasing leukocytic infiltration into the synovial fluid and overt pathology of the joint). However, adenoviral doses of 7 X 10^7 pfu or less produced no detectable leukocytic infiltrate into synovial fluid for up to 14 days post injection and maintained high levels of gene expression (example XVII, particularly col. 37, line 66 continues to line 8 of col. 38).

Glorioso et al. do not specifically teach the use of viral particles comprising a nucleic acid sequence encoding an equine interleukin-1 receptor antagonist protein, or a method of treatment wherein the treated mammal is a horse.

However, at the effective filing date of the present application, Kato et al. already cloned and characterized a cDNA encoding for an equine interleukin-1 receptor antagonist protein (eqIRAP) to establish a basis for cytokine therapy of acute and chronic inflammatory diseases in the horse (see abstract). The eqIRAP shares conserved structural similarities with human, murine and rabbit IRAPs and therefore eqIRAP shares the basic biological functions that IRAPs exhibit in the other species. EqIRAP was shown to inhibit the cytostatic or cytotoxic activity of IL-1 on human A375S2 cell line. Kato et al. further teach that equine IRAP cDNA and recombinant protein could be useful not only for investigating equine inflammatory diseases but also for treatment by administering the recombinant IRAP and IRAP gene transfer, particularly because arthritis is a serious problem in racing and riding horses (page 229, third full paragraph).

Accordingly, it would have been obvious for an ordinary skilled artisan at the effective filing date of the present application to modify the methods taught by Glorioso et al. by delivering *in vivo* a recombinant viral vector encoding an equine IRAP into a mammal or a horse for treatment purposes or for investigation of equine inflammatory diseases in light of the teachings of Kato et al. because equine IRAP shares the basic biological functions as other IRAPs from other species, and that arthritis is a particularly serious problem in racing and riding horses. The modified methods resulting from the combined teachings of Glorioso et al. and Kato et al. are indistinguishable from the methods of the presently claimed invention in terms of the method steps and starting materials.

An ordinary skilled artisan would have been motivated to carry out the above modification because IL-1 receptor antagonist (IRAP) is recognized as a potent anti-inflammatory agent and Glorioso et al. specifically teach the use of any interleukin-1 receptor antagonist gene, fragment or its derivatives as long as its encoded protein, fragment or derivatives can still function in the same manner as the wild type IRAP. Furthermore, Kato et al. already teach that equine IRAP shares the basic biological functions as other IRAPs from other species. Additionally, arthritis is a particularly serious problem in racing and riding horses.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Glorioso et al. and Kato et al., as well as a high level of skill of an ordinary artisan in the art of intra-articular injection of a recombinant vector comprising a sequence encoding IRAP into a mammal.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Examiner would like to cite the following issued U.S. Patents: Glorioso et al. (U.S. 6,228,356), Glorioso et al. (U.S. 6,156,304) and Glorioso et al. (U.S. 5,858,355) are cited to show the state of the art on the delivery of a recombinant vector comprising a sequence encoding IRAP into a joint of a mammal at the effective filing date of the present application.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636, Central Fax No. (703) 872-9306.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER